

What is claimed is:

1. A method for labeling a molecule, comprising the steps of:

(a) contacting a sample molecule with a solid support coupled to a chemical group comprising a cleavable functional group, one or more functional groups, and a reactive group for said sample molecule, under conditions allowing said sample molecule to covalently bind to said reactive group; and

10 (b) cleaving said cleavable functional group, thereby releasing said sample molecule comprising said one or more functional groups.

2. The method of claim 1, wherein said sample molecule is selected from the group consisting of a polypeptide, a nucleic acid, a lipid, a second messenger, and a metabolite.

15 3. The method of claim 1, wherein said sample molecule is a polypeptide.

4. The method of claim 3, wherein said polypeptide has a modification selected from the group consisting of phosphorylation, glycosylation, ubiquitination, acetylation, prenylation, palmitylation, myristylation, sulfation, and hydroxylation.

20 5. The method of claim 4, wherein said polypeptide is a phosphoprotein.

6. The method of claim 1, wherein said solid support is a glass bead.

7. The method of claim 1, wherein said cleavable functional group is a chemical linker cleavable by light, an acid, a base or an enzyme.

8. The method of claim 1, wherein one of said functional groups is a tag.

9. The method of claim 8, wherein said tag is a mass spectrometry tag.

10 10. The method of claim 8, wherein said tag is selected from the group consisting of a stable isotope tag, an isotope distribution tag, and a charged amino acid.

11. The method of claim 10, wherein said tag is a stable isotope coded amino acid.

15 12. The method of claim 11, wherein said tag is a deuterated or non-deuterated amino acid.

13. The method of claim 8, wherein said tag is a gas-phase basic group or a hydrophobic group.

20 14. The method of claim 13, wherein said gas-phase basic group is pyridyl.

15. The method of claim 8, wherein said tag is selected from a fluorophore, chromophore, and spin label.

16. The method of claim 8, wherein one of said functional groups comprises an element having a characteristic isotope distribution.

17. The method of claim 16, wherein said element 5 is chlorine or bromine.

18. The method of claim 3, wherein said reactive group of said chemical group is selected from the group consisting of a succinimide ester group and an iodoacetyl group.

10 19. The method of claim 3, wherein a primary amine group of said polypeptide is modified by treatment with N-succinimidyl S-acetylthioacetate, hydroxylamine, and tris(2-carboxyethyl)phosphine.

15 20. The method of claim 4, wherein said polypeptide is isolated using an antibody having specific binding activity to said modification of said polypeptide.

21. The method of claim 1, wherein the method steps are performed by an automated process.

20 22. The method of claim 1, wherein at least 50 percent of said sample molecule contacted with said solid support is released.

23. A method for analyzing a sample molecule, comprising the steps of:

- (a) contacting a sample molecule with a solid support coupled to a chemical group comprising a cleavable functional group, one or more functional groups, and a reactive group for said sample molecule, under conditions allowing said sample molecule to covalently bind to said reactive group;
- (b) cleaving said sample molecule from said solid support, wherein one or more specific functional groups are transferred to the released sample molecule; and
- (c) analyzing said released sample molecule.

24. The method of claim 23, wherein the released sample molecule is analyzed by mass spectrometry.

15 25. The method of claim 23, wherein a plurality of a class of molecules expressed by a cell or tissue is analyzed.

20 26. The method of claim 23, wherein said sample molecule is selected from the group consisting of a polypeptide, a nucleic acid, a lipid, a second messenger, and a metabolite.

27. The method of claim 26, wherein said sample molecule is a polypeptide.

28. The method of claim 27, wherein said polypeptide has a modification selected from the group consisting of phosphorylation, glycosylation, ubiquitination, acetylation, palmitylation, prenylation, 5 sulfation, hydroxylation, and myristylation.

29. The method of claim 28, wherein said polypeptide is a phosphopolypeptide.

30. The method of claim 23, wherein said solid 10 support is a glass bead.

31. The method of claim 23, wherein said cleavable functional group is a chemical linker cleavable by light, an acid, a base or an enzyme.

32. The method of claim 23, wherein one of said 15 functional groups is a tag.

33. The method of claim 32, wherein said tag is a mass spectrometry tag.

34. The method of claim 32, wherein said tag is selected from the group consisting of a stable isotope tag, 20 an isotope distribution tag, and a charged amino acid.

35. The method of claim 34, wherein said tag is a stable isotope coded amino acid.

36. The method of claim 35, wherein said tag is a deuterated or non-deuterated amino acid.

37. The method of claim 32, wherein said tag is a gas-phase basic group or hydrophobic group.

38. The method of claim 37, wherein said
5 gas-phase basic group is pyridyl.

39. The method of claim 32, wherein said tag is selected from a fluorophore, chromophore, and spin label.

40. The method of claim 32, wherein one of said functional groups comprises an element having a
10 characteristic isotope distribution.

41. The method of claim 40, wherein the elements are chlorine or bromine.

42. The method of claim 23, wherein said reactive group of said chemical group is selected from the group
15 consisting of a succinimide ester group and an iodoacetyl group.

43. The method of claim 27, wherein a primary amine group of said polypeptide is modified by treatment with N-succinimidyl S-acetylthioacetate, hydroxylamine, and
20 tris(2-carboxyethyl)phosphine.

44. The method of claim 28, wherein said polypeptide is isolated using an antibody having specific binding activity to said modification of the polypeptide.

45. The method of claim 23, wherein the method
25 steps are performed by an automated process.

46. The method of claim 23, wherein at least 50 percent of said sample molecule contacted with said solid support is released.

47. The method of claim 23, wherein molecules
5 from two or more samples are comparatively analyzed.

48. The method of claim 47, wherein said two or more samples are differentially labeled.

49. The method of claim 48, wherein said samples are differentially labeled with a mass spectrometry tag.

10 50. The method of claim 48, wherein said samples are differentially labeled with a stable isotope tag, an isotope distribution tag, or a charged amino acid.

15 51. The method of claim 48, wherein said samples are differentially labeled with a fluorophore, chromophore, or spin label.

52. A method for labeling a molecule, comprising the steps of:

(a) contacting a sample molecule with a solid support coupled to a chemical group comprising a cleavable functional group, one or more functional groups, and a reactive group for said sample molecule, under conditions allowing said sample molecule to covalently bind to said reactive group;

10 (b) modifying said sample molecule bound to said solid support; and

(c) cleaving said cleavable functional group, thereby releasing said modified sample molecule comprising said one or more functional groups.

15 53. The method of claim 52, wherein said modifying step is a chemical or enzymatic modification.

54. The method of claim 52, wherein said sample molecule is selected from the group consisting of a polypeptide, a nucleic acid, a lipid, a second messenger, and a metabolite.

20 55. The method of claim 52, wherein said sample molecule is a polypeptide.

56. The method of claim 55, wherein said polypeptide has a modification selected from the group consisting of phosphorylation, glycosylation,

ubiquitination, acetylation, prenylation, palmitylation, myristylation, sulfation, and hydroxylation.

57. The method of claim 56, wherein said polypeptide is a phosphopolypeptide.

5 58. The method of claim 57, wherein said modifying step modifies a phosphate group on said phosphopolypeptide.

59. The method of claim 52, wherein said solid support is a glass bead.

10 60. The method of claim 52, wherein said cleavable functional group is a chemical linker cleavable by light, an acid, a base or an enzyme.

61. The method of claim 52, wherein one of said functional groups is a tag.

15 62. The method of claim 61, wherein said tag is a mass spectrometry tag.

63. The method of claim 61, wherein said tag is selected from the group consisting of a stable isotope tag, an isotope distribution tag, and a charged amino acid.

20 64. The method of claim 63, wherein said tag is a stable isotope coded amino acid.

65. The method of claim 64, wherein said tag is a deuterated or non-deuterated amino acid.

66. The method of claim 61, wherein said tag is a gas-phase basic group or a hydrophobic group.

67. The method of claim 66, wherein said 5 gas-phase basic group is pyridyl.

68. The method of claim 61, wherein said tag is selected from a fluorophore, chromophore, and spin label.

69. The method of claim 61, wherein one of said functional groups comprises an element having a 10 characteristic isotope distribution.

70. The method of claim 69, wherein said element is chlorine or bromine.

71. The method of claim 55, wherein said reactive group of said chemical group is selected from the group 15 consisting of a succinimide ester group and an iodoacetyl group.

72. The method of claim 55, wherein a primary amine group of said polypeptide is modified by treatment with N-succinimidyl S-acetylthioacetate, hydroxylamine, and 20 tris(2-carboxyethyl)phosphine.

73. The method of claim 56, wherein said polypeptide is isolated using an antibody having specific binding activity to said modification of said polypeptide.

74. The method of claim 52, wherein the method 25 steps are performed by an automated process.

75. The method of claim 52, wherein at least 50 percent of said sample molecule contacted with said solid support is released.

76. A composition comprising a solid support
5 coupled to a chemical group comprising a cleavable functional group, a tag and a reactive group covalently linked to a sample molecule, wherein said cleavable functional group, said tag and said reactive group are positioned relative to each other to allow transfer of said
10 tag to said sample molecule upon cleavage of said cleavable functional group.
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77. The composition of claim 76, wherein said sample molecule is selected from the group consisting of a polypeptide, a nucleic acid, a lipid, a second messenger,
15 and a metabolite.

78. The composition of claim 77, wherein said sample molecule is a polypeptide.

79. The composition of claim 78, wherein said polypeptide has a modification selected from the group
20 consisting of phosphorylation, glycosylation, ubiquitination, acetylation, palmitylation, prenylation, sulfation, hydroxylation, and myristylation.

80. The composition of claim 79, wherein said polypeptide is a phosphoprotein.

25 81. The composition of claim 76, wherein the solid support is a glass bead.

82. The composition of claim 76, wherein said cleavable functional group is a chemical linker cleavable by light, an acid, a base or an enzyme.

83. The composition of claim 76, wherein said tag
5 is a mass spectrometry tag.

84. The composition of claim 76, wherein said tag is selected from the group consisting of a stable isotope tag, an isotope distribution tag, and a charged amino acid.

85. The composition of claim 84, wherein said tag
10 is a stable isotope coded amino acid.

86. The composition of claim 85, wherein said tag is a deuterated or non-deuterated amino acid.

87. The composition of claim 76, wherein said tag is a gas-phase basic group or a hydrophobic group.

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88. The composition of claim 87, wherein the gas-phase basic group is pyridyl.

89. The method of claim 76, wherein said tag is selected from a fluorophore, chromophore, and spin label.

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90. The composition of claim 76, wherein said tag comprises an element having a characteristic isotope distribution.

91. The composition of claim 90, wherein said element is chlorine or bromine.

92. The composition of claim 76, wherein said covalently linked reactive group is derived from a succinimide ester group or an iodoacetyl group.

93. The composition of claim 78, wherein a
5 primary amine group of said polypeptide is modified by treatment with N-succinimidyl S-acetylthioacetate, hydroxylamine, and tris(2-carboxyethyl)phosphine.

94. A composition comprising a solid support covalently coupled to a chemical group comprising a
10 cleavable functional group, a mass spectrometry tag and a reactive group for covalently attaching a sample molecule, wherein said cleavable functional group, said tag and said reactive group are positioned relative to each other to allow transfer of said tag to said sample molecule upon
15 cleavage of said cleavable functional group.

95. The composition of claim 94, wherein the solid support is a glass bead.

96. The composition of claim 94, wherein said cleavable functional group is a chemical linker cleavable by
20 light, an acid, a base or an enzyme.

97. The composition of claim 94, wherein said tag is selected from the group consisting of a stable isotope tag, an isotope distribution tag, and a charged amino acid.

98. The composition of claim 97, wherein said tag
25 is a stable isotope coded amino acid.

99. The composition of claim 98, wherein said tag is a deuterated or non-deuterated amino acid.

100. The composition of claim 94, wherein said tag is a gas-phase basic group or a hydrophobic group.

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101. The composition of claim 100, wherein said gas-phase basic group is pyridyl.

102. The method of claim 94, wherein said tag is selected from a fluorophore, chromophore, and spin label.

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103. The composition of claim 94, wherein said tag comprises an element having a characteristic isotope distribution.

104. The composition of claim 103, wherein said element is chlorine or bromine.

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105. The composition of claim 94, wherein said reactive group of said chemical group is selected from the group consisting of a succinimide ester group and an iodoacetyl group.